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ORIGINAL CONTRIBUTION

Gender differences in the prevalence, comorbidities and antipsychotic prescription of early-onset schizophrenia: a nationwide population-based study in Taiwan

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Abstract

Early-onset schizophrenia (EOS) is defined as patients diagnosed with schizophrenia before the age of 18. Whether the EOS population has gender differences is currently a matter of considerable debate. This study used a representative nationwide sample to examine potential gender differences in the prevalence, comorbidities, and prescription of antipsychotics among the EOS population. We identified a total of 401 patients with EOS (200 males and 201 females) from Taiwan's National Health Insurance Database between 2000 and 2012. The annual prevalence rate of overall patients with EOS increased significantly from 17.1 to 41.8 per 100,000 persons among the youth population (≤ 18 years). Sulpiride, Risperidone, and Aripiprazole were the most common antipsychotics of first choice for treating EOS. Compared to female patients, male patients were more likely to experience the following comorbidities: attention deficit hyperactivity disorder (15.5% vs. 5.5%), autism spectrum disorder (10.0% vs. 3.0%), intellectual disability (19.0% vs. 10.4%), developmental disorder (8.0% vs. 3.0%), and history of physical injury (65.5% vs. 48.8%), prior to being diagnosed with schizophrenia. We observed no significant gender differences with regard to incidence, prevalence, age of onset, and categories and doses of patients' first antipsychotic prescription. Our findings did not support the empirical opinion that males with EOS experience the onset earlier or are more prevalent than EOS female patients. However, male patients were more likely to have neurodevelopmental comorbidities and a history of physical injury. These results can function as an important reference for planning services that target real-world patient treatment.

Keywords Early-onset schizophrenia · Gender difference · Incidence · Prevalence · Comorbidity · Antipsychotic

Introduction

Schizophrenia is a brain disorder characterized by cluster symptoms of hallucinations, delusions, irrelevant speech, disorganized behavior, and low motivation [1]. Early-onset schizophrenia (EOS) is defined as schizophrenia developed before the age of 18, either during childhood or adolescence [2]. Compared to schizophrenia onset in adulthood, EOS is somewhat rare and is usually accompanied by more severe premorbid neurodevelopmental abnormalities and larger cognitive function deficits [3–5]. Previous studies have reported gender differences in the pathogenesis and prognosis of EOS [6–8]. Investigating gender differences among

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EOS characteristics can provide crucial clues for research into underlying etiology and treatment strategies.

The lifetime prevalence of schizophrenia is about 1% over the whole population [9], and approximately 4% of all cases of schizophrenia onset before the age of 18 [10]. With regard to gender difference in the incidence or prevalence of EOS, findings in present studies are mixed and inconsistent. Earlier studies demonstrated that EOS is more prevalent in males, whereas recent literature indicated that boys and girls are about equally represented [11]. A retrospective study using the South Carolina Medicaid claims database revealed that the EOS cohort was primarily male (64%) [12]. However, a Denmark study which investigated the incidence of schizophrenia in the period between 2000 and 2012 indicated that the EOS incidence among girls increased more than among boys [13].

Moreover, whether there are gender differences in clinical characteristics among EOS is still controversial. For example, males with EOS had been suggested to have an earlier age of onset than their female counterparts [14]. But a nationwide study showed that the ages of onset were not significantly different between male and female EOS patients [15]. A large part of EOS patients has developmental problems (mostly social) and clear prodromal symptoms [16]. Several studies indicate that schizophrenia is highly associated with autism, attention-deficit hyperactivity disorders (ADHD), Tourette's Syndrome, and affective symptoms [17–20]. And aforementioned comorbidities may have gender differences in prevalence or clinical manifestations. However, current literature that compared the gender differences in the psychiatric comorbidities of EOS is still scarce. Only one study revealed that males with childhood-onset-schizophrenia (COS) had a younger age of onset than females with COS, and had higher rates of comorbid pervasive developmental disorder and ADHD [6]. Furthermore, psychosis in male adult was associated with a high percentage of physical abuse in childhood [21]; therefore, the relationship between a history of physical injury and EOS requires further study.

In addition to studying EOS characteristics, examining the medical treatment of this condition is also vital. Several meta-analysis studies have investigated the effectiveness and safety profiles of antipsychotic treatment in patients with EOS [22–24]. In general, the current evidence indicates that all antipsychotics are superior to a placebo for reducing psychotic symptoms [22–24], with Olanzapine and Risperidone being particularly effective for improving both positive psychotic symptoms and overall symptoms [24]. Meanwhile, Clozapine is considered an effective and generally safe choice for treating refractory EOS [25]. Of particular importance, youths appear to have a greater risk than adults for experiencing adverse effects when taking antipsychotic medication [26]. Various antipsychotics have distinct adverse effect profiles (e.g., extrapyramidal symptoms, weight gain, metabolic effects, and prolactin elevation), which must be considered when determining an individualized treatment decision [27–31]. For example, in view of the side effects of irregular menses and hyperprolactinemia, a high potency antipsychotic may be less favorable for treating female EOS patients [31]. However, little is known about physicians' prescription patterns of initial antipsychotic treatment for patients with EOS in the real world.

To fill the research gap, the aims of this study were to investigate potential gender differences in EOS using a representative nationwide sample from 2000 to 2012 in Taiwan. Specifically, we examine incidence, prevalence, age of onset, psychiatric comorbidities, physical injury, and antipsychotic selection and initial dose among the EOS population.

Methods

Data source

The study used data from the ambulatory claims database of the National Health Insurance Research Database (NHIRD). NHIRD is available from March 1, 1995 for over 1 million randomly sampled enrollees from the National Health Insurance (NHI) program in Taiwan. The NHI Bureau is a single-payer insurance system designed to finance health care for all Taiwanese citizens, and covers 93% of healthcare providers in Taiwan. There are currently over 20 million enrollees in the NHI program. Therefore, the NHIRD is one of the largest datasets in the world, and provides a unique opportunity to investigate the epidemiology among patients with early-onset schizophrenia. The NHIRD data were de-identified, and then provided on application for research purposes. The analysis in the study was approved by the Institutional Review Board (IRB) of Chang Gung Memorial Hospital (IRB no.: 103-0637B).

Study population

We identified all patients who received a diagnosis of schizophrenia by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 295.x, and were prescribed at least one dose of an antipsychotic drug between 2000 and 2012. To ensure the diagnostic validity, the patients were defined as ICD-9-CM code of schizophrenia plus antipsychotic prescription, such a definition has been adopted in previous studies [32, 33]. Further, a patient with EOS was defined as a patient whose age of first positioned diagnosis identified from claim data was under 18. Overall, the study sample consisted of 401 patients, which were then classified according to their gender for further

analysis. Figure 1 illustrated the selection flow chart of EOS and their antipsychotic drug choices.

Incidence, prevalence and patient characteristics

The annual EOS incidence rate was defined as newly diagnosed EOS cases during a year, divided by those under 18 at the end of the year. The annual EOS prevalence rate was identified as schizophrenic patients under 18 at the end of the year divided by those under 18 on the same index date. In total, 200 males and 201 females with EOS were included, and their demographic characteristics and comorbidities were analyzed. We identified patient characteristics, which included age, year of initial diagnosis, neurodevelopmental comorbidities, and past injury history. The neurodevelopmental comorbidities and history of physical injury were defined as any ICD-9-CM before the first diagnosis of schizophrenia from the same medical records. The neurodevelopmental comorbidities included ADHD (ICD-9-CM: 314.x), autism spectrum disorder (ASD, ICD-9-CM: 299.x), intellectual disability (ID, ICD-9-CM: 317.x, 318.x, and 319.x), developmental disorder (DD, ICD-9-CM: 315.x), tic disorder (TD, ICD-9-CM: 307.2), and affective disorder (AD, ICD-9-CM: 296.x); the injury history was defined as any physical injury, including burns, contusion, crushing, dislocation, fracture, injury, sprains, strains, and open wound (ICD-9-CM: 800.x-959.x).

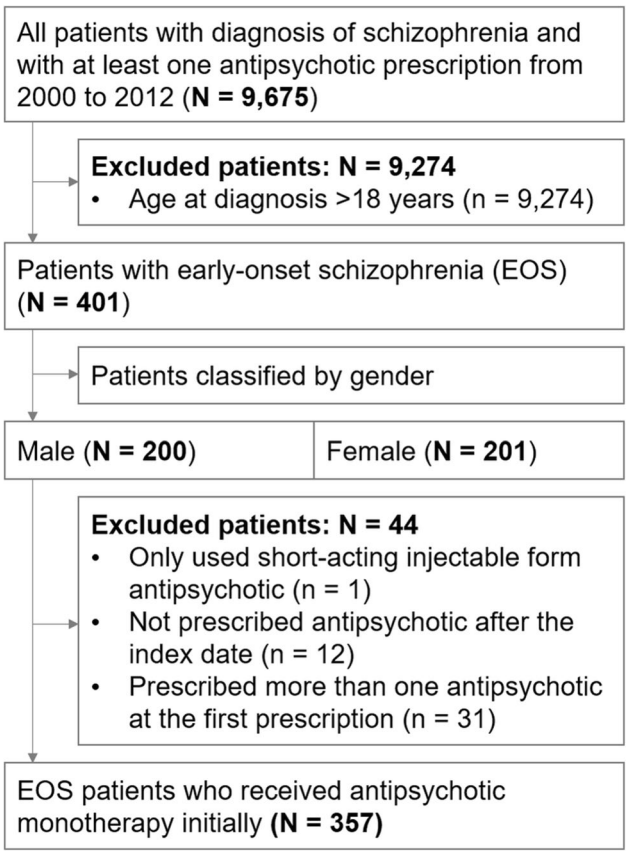

Fig. 1 Flowchart showing the selection procedure of study subjects

First antipsychotic prescription

To investigate the antipsychotic selection, we established the following exclusion criteria: (1) patients who only used the short-acting injectable form of an antipsychotic agent in their lifetime (never prescribed with antipsychotics in long-acting injectable or oral form) ($N = 1$); (2) patients who were not prescribed an antipsychotic agent after the diagnostic date ($N = 12$); and (3) patients who were prescribed more than one antipsychotic agent at the diagnostic date ($N = 31$). Using the selective criteria, 357 patients with antipsychotic prescriptions were further analyzed. In addition to the age and year on the prescribed date, we listed a total of 17 different types of antipsychotic agents from the NHI claim records, including Sulpiride ($N = 132$), Risperidone ($N = 101$), Aripiprazole ($N = 28$), Haloperidol ($N = 18$), Amisulpride ($N = 14$), Olanzapine ($N = 14$), Quetiapine ($N = 13$), Trifluoperazine ($N = 10$), Flupentixol ($N = 7$), Prochlorperazine ($N = 5$), Zotepine ($N = 4$), Ziprasidone ($N = 3$), Chlorpromazine ($N = 2$), Paliperidone ($N = 2$), Thioridazine ($N = 2$), Clozapine ($N = 1$), and Loxapine ($N = 1$). We selected seven different types of antipsychotic agent and their average starting dose (SD) to compare the differences by gender. The SD was defined as the dose of antipsychotic on the day of diagnosis. Moreover, we were interested in a low or high SD between different antipsychotics; therefore, we calculated SD and defined daily dose (DDD) ratios to evaluate it. The DDD is a standardized unit of measurement in pharmacological studies, defined by average maintenance dose of a drug in adults [34]. We used the ratio of SD/DDD in an attempt to normalize the SD to make the comparison of SD between different types of antipsychotics possible. Besides, we also investigated the characteristics and antipsychotics of the 31 patients who were prescribed antipsychotic polypharmacy at the diagnostic date.

Statistical analysis

The Statistical Package for Social Sciences version 22 (SPSS Inc., Chicago, IL, USA) and MedCalc Statistical Software version 17.8 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2017) were used to perform the analyses in the study. Differences in the annual incidence or prevalence were compared among patients with different a gender or year via the general linear model using the linear trend. Pearson Chi-squared tests or independent sample t tests were carried out to examine the differences in demographic characteristics, comorbidities, and antipsychotic

prescriptions between male and female groups. A significant level of $p < 0.05$ was adopted for the study.

Results

Figure 2 shows the incidence and prevalence of EOS by gender from 2000 to 2012. The annual incidence rate was between 8.4 and 26.4 per 100,000 persons, and the average annual incidence rate during the study period was 15.1 per 100,000 persons (14.6 for males and 15.7 for females). During the study period, no significant difference in EOS incidence rate was found between the genders ($t = 0.896$, $p = 0.370$), and the incidence rate did not change significantly over time ($t = -1.104$, $p = 0.270$). However, the overall trend of the EOS prevalence rate significantly increased from 2000 (17.1 per 100,000 persons) to 2012 (41.8 per 100,000 persons) ($t = 3.532$, $p < 0.001$). The average annual prevalence rate was 28.8 per 100,000 persons during the study period, and there was no significant gender difference in prevalence during the study period (29.8 for males and 27.7 for females, $t = 1.348$, $p = 0.178$).

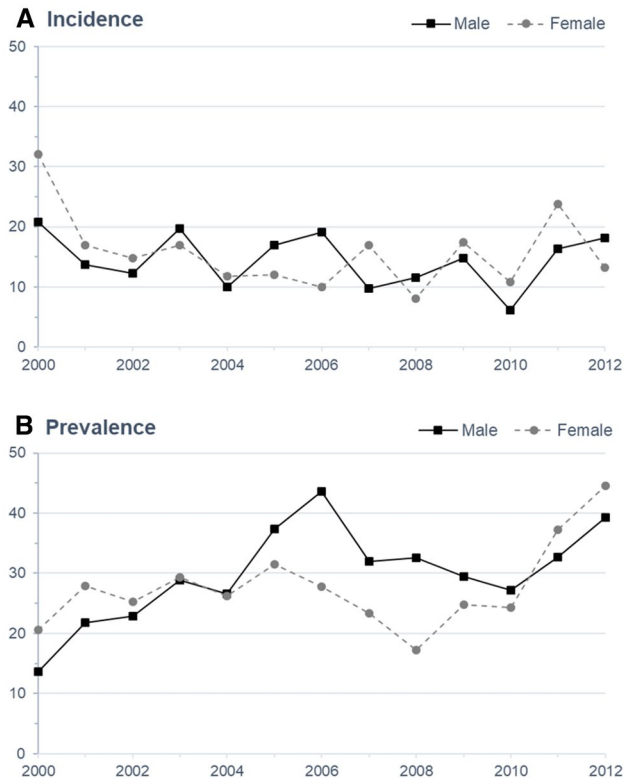

Fig. 2 Annual incidence and prevalence rates of early-onset schizophrenia (EOS) stratified by gender in Taiwan between 2000 and 2012. The *y*-axis represents the incidence or prevalence of EOS (per 100,000) in each year, the *x*-axis between 2000 and 2012. **a** Annual incidence rate; **b** annual prevalence rate

Table 1 shows the comparison of demographic characteristics and comorbidities between male and female patients with EOS. Among the overall 401 EOS patients, the mean age on the first diagnostic date was 15.76 years. We found no significant gender difference in age of initial diagnosis (15.63 years for males, 15.88 years for females). Male patients had higher rates of neurodevelopmental comorbidities of ADHD ($\chi^2 = 10.72$, $p = 0.001$), ASD ($\chi^2 = 8.12$, $p = 0.004$), ID ($\chi^2 = 5.83$, $p = 0.016$), and DD ($\chi^2 = 4.85$, $p = 0.028$) in comparison to female patients. The male group was more likely to have a history of physical injury ($\chi^2 = 11.45$, $p = 0.001$) than the female group. Moreover, there were no gender differences in tic disorder ($\chi^2 = 0.21$, $p = 0.649$) and affective disorder ($\chi^2 = 2.86$, $p = 0.091$).

There were 357 patients (178 males and 179 females) who were prescribed antipsychotics with an initial monotherapy. Table 2 lists the prescription patterns of these patients. The daily dose at the first prescription and ratio of SD–DDD among the seven most commonly prescribed antipsychotics were Sulpiride (346.75 ± 234.73 mg, 0.43 ± 0.29), Risperidone (1.68 ± 1.04 mg, 0.34 ± 0.21), Aripiprazole (6.93 ± 4.05 mg, 0.46 ± 0.27), Haloperidol (8.04 ± 13.79 mg, 1.00 ± 1.72), Amisulpride (250.34 ± 115.56 mg, 0.63 ± 0.29), Olanzapine (6.84 ± 3.53 mg, 0.68 ± 0.35), and Quetiapine (71.15 ± 65.23 mg, 0.18 ± 0.16), respectively. There were no significant gender differences in the choice of antipsychotic or dosing at the initial prescription. Moreover, the ratio of SD–DDD of these antipsychotics were mostly less than 0.7 except Haloperidol.

Besides, Supplement Table 1 shows the comparative characteristics between patients who were prescribed antipsychotic with monotherapy and polypharmacy. Except history of physical injury (monopharmacy: 58.3% vs. polypharmacy: 38.7%, $\chi^2 = 4.43$, $p = 0.035$), we found that the characteristics of patients who were prescribed mono-antipsychotic at the first prescription were non-significantly different from those with multiple antipsychotic treatment. Supplement Table 2 shows the clinical characteristics and antipsychotics use of patients with polypharmacy, only Risperidone use had a significant difference with the female predominance ($\chi^2 = 11.14$, $p = 0.001$).

Discussion

Incidence, prevalence and age of onset

The mean annual incidence of EOS between 2000 and 2012 in our study was 15.1 per 100,000 persons. Comparable with our finding, previous database studies in US and Canada reported that the incidence of EOS was less than 40 per 100,000 people per year [12, 35]. Our study found no obvious change of incidence during the 13 years of the study

Table 1 Characteristics of patients with early-onset schizophrenia by genders from 2000 to 2012 in Taiwan

Characteristics	Overall ($N = 401$)	Male ($N = 200$)	Female ($N = 201$)	Statistics	p
Gender					
Male	200 (49.9)	200 (100.0)	–		
Female	201 (50.1)	–	201 (100.0)		
Age at diagnosis (years)	15.76 ± 1.83	15.63 ± 1.98	15.88 ± 1.66	t (1.37)	0.171
Age range (years)	6.57 to 18.00	6.57 to 18.00	10.14 to 17.98		
12 ≤ age	15 (3.7)	9 (4.5)	6 (3.0)		
12 < age ≤ 18	386 (96.3)	191 (95.5)	195 (97.0)		
Initiation year				χ^2 (12.87)	0.379
2000 or prior to 2000	68 (17.0)	28 (14.0)	40 (19.9)		
2001	37 (9.2)	17 (8.5)	20 (10.0)		
2002	32 (8.0)	15 (7.5)	17 (8.5)		
2003	43 (10.7)	24 (12.0)	19 (9.5)		
2004	25 (6.2)	12 (6.0)	13 (6.5)		
2005	33 (8.2)	20 (10.0)	13 (6.5)		
2006	31 (7.7)	21 (10.5)	10 (5.0)		
2007	26 (6.5)	10 (5.0)	16 (8.0)		
2008	18 (4.5)	11 (5.5)	7 (3.5)		
2009	27 (6.7)	13 (6.5)	14 (7.0)		
2010	13 (3.2)	5 (2.5)	8 (4.0)		
2011	28 (7.0)	12 (6.0)	16 (8.0)		
2012	20 (5.0)	12 (6.0)	8 (4.0)		
Comorbidities					
ADHD	42 (10.5)	31 (15.5)	11 (5.5)	χ^2 (10.72)	0.001**
Autism spectrum disorder	26 (6.5)	20 (10.0)	6 (3.0)	χ^2 (8.12)	0.004**
Intellectual disability	59 (14.7)	38 (19.0)	21 (10.4)	χ^2 (5.83)	0.016*
Developmental disorder	22 (5.5)	16 (8.0)	6 (3.0)	χ^2 (4.85)	0.028*
Tic disorder	5 (1.2)	3 (1.5)	2 (1.0)	χ^2 (0.21)	0.649
Affective disorder	84 (20.9)	35 (17.5)	49 (24.4)	χ^2 (2.86)	0.091
Injury history	229 (57.1)	131 (65.5)	98 (48.8)	χ^2 (11.45)	0.001**

Data were expressed by N (%) or mean ± standard deviation; statistic values were expressed by Pearson's χ^2 or t by independent t test

ADHD attention deficit hyperactivity disorder

*$p < 0.05$; **$p < 0.01$

period. In contrast, a study in Denmark indicated increasing incidence of EOS from 1971 to 2010 [15]. The increased incidence of EOS in Denmark might be explained by better implementation of the diagnostic criteria for schizophrenia in child and adolescent psychiatry and improved access to early intervention services in past decades [13]. However, the duration in our study was relatively short, and it reduced the statistical power to detect potential changes of EOS incidence. Future studies with a longer follow-up are needed to investigate the trend of EOS incidence.

The study herein revealed that the overall trend of EOS prevalence in Taiwan elevated between 2000 and 2012. The underlying reason for the significant upward trend needs to be further explored. One possibility is that the numbers of newborns in Taiwan persistently deceased in the past two decades. Therefore, the total population of child and adolescent (denominator) decreased, and the incident cases of EOS (numerator) remained steady. The EOS prevalence naturally increased. Intriguingly, a study in China also found that the prevalence of overall schizophrenia doubled between 1990 and 2010 [36], and the phenomenon was proposed to be associated with social environmental changes (i.e., urbanization). It is noteworthy that the prevalence herein only represented the diagnostic rates (patients who had diagnosis records in NHI). Obtaining the actual incidence/prevalence of EOS must be throughout a face-to-face diagnostic interview for a representative sample. Hence, it would be cautious to make international comparisons of incidence or prevalence of EOS.

No significant gender differences in incidence or prevalence were observed in our group. A review article indicated that rate ratio for males/females was 1.4:1 in overall

Table 2 Antipsychotic prescription and their initial dose for patients with early-onset schizophrenia

Characteristics	Overall ($N = 357$)	Male ($N = 178$)	Female ($N = 179$)	Statistics	p
Age at prescription (years)	15.85 ± 1.84	15.78 ± 2.01	15.93 ± 1.67	t (0.73)	0.466
Drug classification				χ^2 (8.39)	0.300
Sulpiride	132 (37.0)	64 (36.0)	68 (38.0)	χ^2 (0.12)	0.728
Dose (mg/day)	346.75 ± 234.73	351.11 ± 218.55	342.65 ± 250.57	t (− 0.21)	0.837
SD/DDD ratio	0.43 ± 0.29	0.44 ± 0.27	0.43 ± 0.31		
Risperidone	101 (28.3)	51 (28.7)	50 (27.9)	χ^2 (0.01)	0.921
Dose (mg/day)	1.68 ± 1.04	1.57 ± 0.76	1.79 ± 1.25	t (1.10)	0.276
SD/DDD ratio	0.34 ± 0.21	0.31 ± 0.15	0.36 ± 0.25		
Aripiprazole	28 (7.8)	9 (5.1)	19 (10.6)	χ^2 (3.57)	0.059
Dose (mg/day)	6.93 ± 4.05	8.29 ± 3.53	6.28 ± 4.21	t (− 1.24)	0.227
SD/DDD ratio	0.46 ± 0.27	0.55 ± 0.24	0.42 ± 0.28		
Haloperidol	18 (5.0)	8 (4.5)	10 (5.6)	χ^2 (0.22)	0.637
Dose (mg/day)	8.04 ± 13.79	9.85 ± 20.34	6.59 ± 5.67	t (− 0.44)	0.672
SD/DDD ratio	1.00 ± 1.72	1.23 ± 2.54	0.82 ± 0.71		
Amisulpride	14 (3.9)	9 (5.1)	5 (2.8)	χ^2 (1.14)	0.285
Dose (mg/day)	250.34 ± 115.56	222.22 ± 97.18	300.95 ± 139.74	t (1.25)	0.236
SD/DDD ratio	0.63 ± 0.29	0.56 ± 0.24	0.75 ± 0.35		
Olanzapine	14 (3.9)	10 (5.6)	4 (2.2)	χ^2 (2.57)	0.109
Dose (mg/day)	6.84 ± 3.53	6.07 ± 2.84	8.75 ± 4.79	t (1.32)	0.212
SD/DDD ratio	0.68 ± 0.35	0.61 ± 0.28	0.88 ± 0.48		
Quetiapine	13 (3.6)	6 (3.4)	7 (3.9)	χ^2 (0.08)	0.782
Dose (mg/day)	71.15 ± 65.23	79.17 ± 69.67	64.29 ± 65.92	t (− 0.40)	0.700
SD/DDD ratio	0.18 ± 0.16	0.20 ± 0.17	0.16 ± 0.16		
Others (10 kinds)	37 (10.4)	21 (11.8)	16 (8.9)	χ^2 (0.68)	0.411

Data were expressed by N (%) or mean ± standard deviation; statistic values were expressed by Pearson's χ^2 or t by independent t test

SD starting dose, *DDD* defined daily dose

*$p < 0.05$; **$p < 0.01$

schizophrenia patients [37]. Furthermore, a nationwide study in Denmark found that male–female ratio of EOS was between 0.8 and 1 from 2002 to 2012; nonetheless, the male–female ratio among adult schizophrenia was between 1.2 and 1.8 [13]. However, the current study suggested that incidence or prevalence of EOS was not significantly different in Taiwan. In addition, previous evidence suggested a gender difference in age of onset among overall patients with schizophrenia. It has been suggested that men usually develop the illness before age 25, while the mean age of onset in women is after age 25 [38]. But among the population with EOS, gender difference in age of onset was not observed in a nationwide survey in Denmark [15], and our national group also showed a comparable finding.

Neurodevelopmental comorbidity and injury history

We found the comorbidity rates of ADHD (10.5%), ASD (6.5%), ID (14.7%), and DD (5.5%) among the EOS population were much higher than the corresponding prevalence rate of each illness in Taiwan [39–42]. And the males with EOS have significantly higher rates of these comorbidities than females. One cross-sectional study also found that among patients with COS, males have higher rates of comorbid pervasive developmental disorder and ADHD than female ones [6]. A study conducted in Australia indicated that females have better premorbid functioning than males in schizophrenia [37]. Some brain imaging studies showed that schizophrenia, ADHD, ASD, and ID shared similar deficits of brain connectivity linking regions related to cognitive functions (e.g., the default mode network and executive function) [43]. Taken together with the findings in our study, males with EOS may have greater neurodevelopmental vulnerability, or are more externalized to get another diagnosis of neurodevelopmental disorders than their female counterparts [44].

Our results showed that more than a half of patients with EOS had a history of physical injury (using cluster codes from ICD-9), with significant male predominance. Past literature indicated that childhood physical trauma (using a questionnaire which included physical abuse and neglect)

had an impact on psychopathology in schizophrenia [45], and interacted with genetic vulnerability to psychosis and other environmental factors [46]. However, ADHD is a male predominant disorder and is significantly associated with increased risk of traumatic injury (using injury mortality diagnosis matrix from the ICD-10) [47]. Therefore, whether the high rates of preceding injury history directly link to the susceptibility of EOS, or some other risk factors (i.e., ADHD or low social economic status) underpinned the correlation between injury history and EOS require further investigation.

Choice and dosing of antipsychotics

We found that the most commonly prescribed antipsychotic agent for EOS in Taiwan was Sulpiride, followed by Risperidone and Aripiprazole. In addition, the initial antipsychotic choice for male EOS was no significant difference in comparison with those for female patients. However, physicians tended to prescribe Aripiprazole more for females with EOS (10.6% in females and 5.1% in males), but the difference did not reach a statistically significant level ($p = 0.059$). Among numerous antipsychotics, Aripiprazole was less associated with hyperprolactinemia-related side effects, including amenorrhea and galactorrhea [48, 49]. Further investigation is required for clarifying whether Aripiprazole is beneficial for drug adherence for females as they need long-term treatment.

To our best knowledge, this is the first study reporting the initial dose of an antipsychotic prescription for EOS in the real world. Our results showed the available dosage data of antipsychotics among those first line clinicians. After these SDs were converted into equal DDD (average dose suggested by WHO), we found that all the prescribed antipsychotics were almost lower than 100% DDD (Table 2). It represents that clinicians usually considered that starting low is a safe strategy in antipsychotic treatment for EOS. Compared to other antipsychotics, Haloperidol was used with a high dose at index date (1 DDD) which may have resulted from the same possibility of that of the injection form Haloperidol for acute psychosis. Moreover, there were no differences of first daily dose in different gender in this study. The finding indicates that physicians did not take gender as a major consideration into initial antipsychotic dosing.

Limitation

The study had some important limitations. First, the diagnosis of schizophrenia was identified based on the ICD-9-CM codes, however, was not validated using face-to-face diagnostic criteria. Clinical validity of diagnoses remains a concern. However, with the EOS patients (more than 80%) that were diagnosed by psychiatrists in this study, diagnostic validity should be fair. Second, NHI data in our study were collected from medical records since 2000. Some EOS patients may have been diagnosed before 2000, but they were still accounted for in the patient population in 2000, which may overestimate the incidence in 2000. Third, our study used reimbursement data, therefore, some important clinical characteristics such as clinical picture, symptom severity, injury cause, life stress, socioeconomic status, or family function, were not provided. It is unclear how the incidence of EOS diagnosis or the decision of prescribing antipsychotics was influenced by the aforementioned factors. Fourth, augmentation with other than antipsychotics, the duration of drug treatment, and drug adherence were not analyzed in this study. Finally, this study was conducted in an Asian population. Our findings in EOS patients may not be extended to other ethnic groups.

Conclusion

Using a nationwide group, our report comprehensively demonstrated no gender differences in the incidence, prevalence, age of onset, and choice and dosing strategy of the initial antipsychotic prescription among EOS patients in Taiwan. However, male patients were more likely than female patients to have neurodevelopmental comorbidities and physical injury history. These results provide new insight into the epidemiology and antipsychotic choices for EOS in the real world, which is crucial for developing services that target patient treatment and aid their medical providers.

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Author contributions CWH participated in interpreting data, reviewing references, and drafting the manuscript. SYL participated in the design of the study. LJW executed the statistical analysis and revised the manuscript.

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Compliance with ethical standards

Ethical standards The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975. The study is approved by the Institutional Review Board of Chang Gung Memorial Hospital (no.: 103-0637B).

Conflict of interest All authors declare no conflicts of interests.

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